THE GENETIC CAUSES OF ATRIAL FIBRILLATION CLASSIFICATION PROPOSAL STATE-OF-THE-ART

Pérez Riera, Andrés Ricardo
Dubner, Sérgio
Schapachnik, Edgardo

Abstract

Atrial fibrillation is the most common type of sustained arrhythmia, mainly in old age. In young people, (age <50 years) it is 1:1,000 persons. With the drastic increase of the discoveries made in the genetic areas, the group of lone atrial fibrillation was increasingly smaller. More often, genetic atrial fibrillation is monogenic and dominant autosomal, affecting several of the potassium channels in phase 3. More rarely it may be recessive autosomal or linked to gender. In this last case, the sodium channel has been reported as being affected.

There are forms with mutations in multiple genes known as familial polygenetic atrial fibrillation.
The genetic atrial fibrillation could be both isolated when associated to channel diseases such as long QT and short QT syndromes, Brugada syndrome, and Catecholaminergic Polymorphic Ventricular Tachycardia. Finally, it can be associated with genetic structural heart disease (genetic cardiomyopathies) such as familial dilated cardiomyopathy, hypertrophic cardiomyopathy, idiopathic Restrictive Cardiomyopathy, Arrhythmogenic Right Ventricular Dysplasia and those unclassified such as Non-Compaction Cardiomyopathy, fibroelastosis and mitochondrial diseases.

Introduction

Atrial fibrillation (AF) is the most common type of sustained arrhythmia, considered, by far, also the most common arrhythmia of man, affecting millions of patients worldwide. In the developed world, it affects 1% to 1.5% of the population. In the United States, more than 3 million people are affected. AF affects one in ten individuals over the age of 80 years, causes significant morbidity, and is an independent predictor of mortality. Projected data from the population-based studies suggest that the prevalence of AF will grow at least 3-fold by 2050 ([1]). The risk of developing this irregular and chaotic electrical activity of the atria increases with age. AF is characterized by uncoordinated electrical activity in the atria (chaotic), which causes the heartbeat to become fast, normal, or slow but always irregular. If untreated, this abnormal heart rhythm can lead to dizziness, chest pain, a sensation of fluttering or palpitations, shortness of breath, or syncope. AF also increases the risk of stroke. Approximately 15% of all strokes are caused by AF. Complications of

familial AF can occur at any age, although some people with this heart condition never experience any health problems associated with the disorder.

Prevalence: The prevalence of AF in the young (age <50 years) is 0.1%, or 1:1,000 persons **([2])**.

Incidence: The incidence of familial AF is unknown; however, recent studies suggest that up to 30% of all people with AF may have a history of the condition in their family.

Age: Lone AF has generally been applied to patients under 60 years of age **([3])**; however, Brand et al**([4])** have included those up to age 65 or even older, who appear to be at increased thromboembolic risk compared to younger patients. Based upon these unresolved issues, the 2006 ACC/AHA/ESC guidelines concluded that there was no standard definition for lone AF **([5])**. The guidelines applied the term to patients under the age 60 without clinical or echocardiographic evidence of heart disease. However, a strict definition may no longer be important because a larger number of patients in addition to those with lone AF are at low risk for thromboembolism.

In general, patients less than 60 years of age with normal left ventricular function and left atrial size have a low risk of thromboembolic events and are unlikely to gain any significant benefit with anticoagulants; however, patients older than 60 years with impaired left ventricular function, enlarged left atrium, and/or associated conditions such as hypertension have an increased risk of thromboembolism and would benefit from long-term anticoagulant therapy. Decisions regarding anticoagulant usage would be simplified by using a scoring system containing clinical and investigational variables **([6])**. The clinical trials that evaluated the efficacy of warfarin and aspirin in patients with AF generally excluded those with lone AF. In the SPAF-I trial, for example, only 51 of 1330 patients (3.8%) were considered to have lone AF **([7])**; however, these trials were able to identify patients over the age of 60 who lacked certain specific high-risk factors (e.g., valvular disease, prior thromboembolism, heart failure or left ventricular dysfunction, hypertension, or in some cases, diabetes) and who had a low risk of thromboembolism on aspirin therapy even though they did not fit a strict definition for lone AF.

Familial background: Lone AF patients have a first-degree family member with AF substantially more often than other AF patients (non-lone AF). This suggests that an inherited trait may be particularly important in this subgroup of patients **([8])**. Kato et al **([9])** identified gene polymorphisms that confer susceptibility to lone AF. The study population comprised 1069 unrelated Japanese individuals, including 196 subjects with chronic lone AF and 873 controls. The genotypes for 40 polymorphisms of 32 candidate genes were determined by a method that combines the polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array

technology. Multivariable logistic regression analysis with adjustment for age, sex, body mass index, and the prevalence of smoking, hypertension, diabetes mellitus, and hypercholesterolemia as well as a stepwise forward selection procedure revealed that the -1306C-->T polymorphism of the matrix metalloproteinase 2 gene (MMP2) and the -592A-->C polymorphism of the interleukin 10 gene (IL10) were significantly (false discovery rate of <0.05) associated with the prevalence of AF. The T allele of the MMP2 polymorphism and the C allele of the IL10 polymorphism were a risk factor for and protective factor against AF, respectively.

Gender: Male predilection for Lone AF is attenuated as the likelihood of dominant Mendelian inheritance increases. Increased frequency of "sporadic" Lone AF among men could be partially due to X-linked recessive inheritance. Sporadic and familial Lone AF are clinically indistinguishable **([10])**. AF is a heritable disorder with male predilection, suggesting a sex chromosome defect in certain patients. Mutation of EMD can underlie X-linked familial AF. Lys37del is associated with epithelial cell emerin deficiency, as in EDMD, yet it causes electrical atriomyopathy in the absence of skeletal muscle disease. Targeted genetic testing of EMD should be considered in patients with SND-associated AF and/or family history suggesting X-linked inheritance. Loss-of-function truncation mutations in EMD, encoding the nuclear membrane protein emerin, cause X-linked Emery-Dreifuss muscular dystrophy (EDMD) characterized by localized contractures and skeletal myopathy in adolescence, sinus node dysfunction in early adulthood, and AF as a variably associated trait. Mutation of Emery-Dreifuss can underlie X-linked familial AF. Lys37del is associated with epithelial cell emerin deficiency, as in EDMD, yet it causes electrical atriomyopathy in the absence of skeletal muscle disease. Targeted genetic testing of EMD should be considered in patients with sinus node dysfunction associated to AF and/or family history suggesting X-linked inheritance **([11])**.

Familial AF appears to be –in major cases- inherited in an autosomal dominant pattern, which means the defective gene is located on an autosomal, and only one copy of the defective gene -inherited from one parent- is sufficient to cause the disorder that causes disruptions in the heart's normal rhythm. Mutations in multiple genes have been implicated in familial AF, but the underlying mechanisms, and thus implications for therapy, remain ill-defined.

In 1997, Ramon Brugada et al **([12])** identified the first locus for familial AF on chromosome 10q22-24 in three different Spanish families. Since that time, several further loci have been mapped by linkage analysis, for monogenetic AF, including: 1-q24.2, 1p36-p35 **([13]),** 4q25 **([14;15])**, 5p13 **([16])**, 5p15 **([17])**, 6q14-16 **([18]),** 7q35-36 **([19])**, 10p11-q21 **([20])**, 11p15.5 **([21])**, 16q22 **([22; 23])**, 17q23 **([24]),** and 21q22.12**([19])**.

Some of these loci encode for subunits of potassium channels.

The ***KCNE2*** and ***KCNJ2*** genes are associated with familial AF. A small percentage of all cases of familial AF are associated with changes in the ***KCNE2*****,** ***KCNJ2*****,** and ***KCNQ1*** genes. These genes provide instructions for making proteins that act as channels across the cell membrane. These channels transport positively charged potassium ions into and out of cells. In heart muscle, the ion channels produced from the *KCNE2*, *KCNJ2*, and *KCNQ1* genes play critical roles in maintaining the heart's normal rhythm. Mutations in these genes have been identified in only a few families worldwide. These mutations increase the activity of the channels, which changes the flow of potassium ions between cells. This disruption in ion transport alters the way the heart beats, increasing the risk of syncope, stroke, and sudden death.

1) **Official Symbol KCNQ1 gene:** Mutations in the *KCNQ1* gene cause familial AF. Recently, Das et al **([25])** identified a family with pseudo-lone AF due to a mutation in the highly conserved S3 domain of KCNQ1, a region of the channel not previously implicated in the pathogenesis of AF. Compared with unaffected family members, those with AF had a longer mean QRS duration (100 vs. 86 ms, P = .015) but no difference in the corrected QT interval (423 +/- 15 ms vs. 421 +/- 21 ms). Mutations in KCNQ1 and Atrial Natriuretic Peptide Precursor (ANPPA) genes led to delayed K^+ rectifier channel I_{Ks} "gain of function", atrial AP shortening, and consequent altered Ca^{2+} current as a common mechanism between diverse familial AF syndromes **([26])**.
2) **Official Symbol KCNE2 gene potassium voltage-gated channel**(Kv)**, Isk-related family, member 2**: channels represent the most complex class of voltage-gated ion channels from both functional and structural standpoints. Their diverse functions include regulating neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction, and cell volume. This gene encodes a member of the potassium channel, voltage-gated, I_{ks}-related subfamily. This member is a small integral membrane subunit that assembles with the KCNH2 gene product, a pore-forming protein, to alter its function. This gene is expressed in heart and muscle and the gene mutations are associated with AF. **Chromosome**: 21; **Location:** 21q22.12**([19])**.
3) **Official Symbol KCNJ2 gene: Name:** potassium inwardly-rectifying channel, subfamily J, member 2. **Other Designations:** cardiac inward rectifier potassium channel; inward rectifier K+ channel KIR2.1; potassium inwardly-rectifying channel J2. **Chromosome:** 17; **Location:** 17q23.1-q24.2
4) **Official Symbol KCNH2 (HERG):** The alpha-subunit of the myocardial I_{kr}-channel, encoded by the KCNH2 gene, is crucial to ventricular and atrial repolarization. Patients with

mutations in KCNH2 present with higher incidence of AF. Common variants in KCNH2 have been shown to modify ventricular repolarization **([27])**.

5) **KCNE5: Official Symbol:** Kcne1 and Name: potassium voltage-gated channel, Iks-related family, member 1-like [*Rattus norvegicus*]. Other Aliases: Kcne5 Other Designations: voltage-gated potassium channel accessory subunit 5. Chromosome: X; Location: Xq14. A missense mutation in KCNE5 may be associated with non-familial or acquired forms of AF. The arrhythmogenic mechanism most likely is a gain of function of I_{Ks}**([28])**.

Block of I_{kur} can provide the substrate for development of AF in healthy canine atria, presumably via abbreviation of action potential duration (APD) and effective refractory period (ERP) can provide the substrate for development of AF in healthy canine atria, presumably via abbreviation of APD and ERP**([29])**. Yang, et al **([30])** identified three novel KCNA5 mutations that were found in 4 of 120 unrelated AF families. Among them, T527M was found in two AF families, and A576V and E610K in two other AF families, respectively. The mutations T527M and A576V were also detected in 2 and 1 of 256 patients with idiopathic AF, respectively. The same mutations were not observed in 200 secondary AF patients and 500 controls. Functional analyses revealed consistent loss-of-function effects of mutant KCNA5 proteins on the ultra-rapidly activating delayed rectifier K^+ currents I_{kur}. These findings expand the spectrum of mutations in KCNA5 linked to AF and provide new insight into the molecular mechanism involved in AF.

Zhang et al **([31])** showed that the specific AF gene underlying this linkage is NUP155, which encodes a member of the nucleoporins, the components of the nuclear pore complex (NPC). Loss of NUP155 function causes AF by altering mRNA and protein transport and link the NPC to cardiovascular disease.

The remaining familial AF affects the Na^+ channel on the SCN5A gene. SCN5A-encoded Na^+ channels have been reported in familial AF. A mechanism of atrial torsade has been suggested to occur in patients with congenital long QT syndrome (LQTS). Compared to the background prevalence of 0.1%, early-onset AF was observed in almost 2% of patients with genetically proven LQTS and should be viewed as an uncommon but possible LQT-related dysrhythmia. Clinical complaints of palpitations warrant thorough assessment in patients with LQTS **([2])**. All potassium and sodium mutations are associated with a gain of function of repolarization potassium or sodium currents, resulting in a shortening of action potential duration(APD), atrial effective refractory period (ARP), and prolonged signal-averaged P-wave duration which facilitate multiple re-entrant circuits in AF**([19])**.

A perturbation of the atrial natriuretic peptide-cyclic guanosine monophosphate (cGMP) pathway in cardiac electrical instability was observed. Hodgson-Zingman et al**(**[13]**)** mapped an AF locus to chromosome 1p36-p35 and identified a heterozygous frameshift mutation causing a 12-amino acid extension to the C terminus of atrial natriuretic peptide (ANP). The frameshift product (fsANP), but not wild-type ANP (wtANP), was elevated in the serum of affected patients, but the molecular basis for the elevated peptide concentrations was not determined.

Mutations in multiple-gene Familial polygenetic predisposition to AF

Several family studies have shown a strong polygenetic predisposition for AF but, so far, most of the linkage analysis and candidate gene studies have discovered only monogenic, rare, deleterious mutations. Recent breakthroughs in high-throughput genotyping technology have allowed improved scanning of the genome with greater statistical power to detect susceptibility alleles for AF. Using this technology, a region on 4q25 has now been identified and validated in thousands of cases as a common susceptibility factor for AF with an odds ratio of over 3.0 for homozygotes. The Paired-like homeodomain transcription factor 2 (PITX2) gene, which is involved in embryonic cardiac development, has been identified as the causal variant for the 4q25 susceptibility locus **(**[32]**)**. This condition is often related to structural abnormalities of the heart or underlying heart disease. Additional risk factors for AF include hypertension, diabetes mellitus, hyperthyroidism, mitral stenosis, a previous stroke, or atherosclerosis of the arteries. Although most cases of AF are not known to run in families, studies suggest that they may arise partly from genetic risk factors. Researchers are working to determine which genetic changes may influence the risk of AF.

Holt-Oram syndrome, also called heart-hand syndrome, is an inherited disorder characterized by abnormalities of the upper limbs and heart. Holt and Oram first described this condition in 1960 in a 4-generation family with atrial septal defects and thumb abnormalities. Mutations in T-box transcription factor 5 (TBX5) underlie this syndrome. Postma et al **(**[33]**)** described a large atypical variant in a family in which affected patients have mild skeletal deformations and paroxysmal AF, but few have congenital heart disease. Sequencing of TBX5 revealed a novel mutation, c.373G>A, resulting in the missense mutation p.Gly125Arg, in all investigated affected family members, cosegregating with the disease. The authors demonstrate that the mutation results in normal Nkx2-5 interaction, is correctly targeted to the nucleus, has significantly enhanced DNA binding and activation of both the Nppa(Anf) and Cx40 promoter, and significantly augments expression of Nppa, Cx40, Kcnj2, and Tbx3 in comparison with wild-type TBX5. Thus, contrary to previously published data, the p.G125R TBX5 mutation results in a gain-of-function. The authors speculate

that the gain-of-function mechanism underlies the mild skeletal phenotype and paroxysmal AF and suggest a possible role of TBX5 in the development of paroxysmal AF based on a gain-of-function either through a direct stimulation of target genes via TBX5 or indirectly via TBX5 stimulated TBX3. These findings may warrant a renewed look at the phenotypes of families and individuals hitherto not classified as HOS or as atypical but presenting with paroxysmal AF, because these may possibly be the result of additional TBX5 gain-of-function mutations.

An involvement of the renin angiotensin system in AF has been hypothesized, and ACE DD genotype has been suggested to influence the predisposition to AF.

Fantini et al **([34])** investigate the role of the ACE I/D polymorphism in relation to the different clinical forms of AF, lone and secondary nonvalvular atrial fibrillation (NVAF). The authors studied 510 consecutive patients with documented NVAF (106 patients had lone, and 404 secondary NVAF), and 520 controls with a negative history of cardiovascular disease. A significant difference in allele frequency between lone and secondary NVAF has been found. The ACE D allele was associated with the predisposition to lone NVAF under a dominant, recessive and additive model, both at univariate and multivariate analysis, after adjustment for age and gender. ACE D allele was significantly associated with secondary NVAF at both univariate and multivariate analysis under a recessive and additive, but not dominant, model. This study highlights the role of the ACE gene in predisposing to both lone and secondary NVAF, further contributing to penetrate the genetic mechanisms responsible for this complex disease. The clinical relevance of these results may be related to the possible characterization of subjects predisposed to NVAF in the absence of traditional risk factors, and to the use of ACE-inhibitors therapy able to improve the arrhythmogenic substrate.

The angiotensin-converting enzyme (ACE) gene contains a common polymorphism based on the insertion (I) or deletion (D) of a 287-bp intronic DNA fragment. The D allele is associated with higher ACE activity and thus higher angiotensin II levels. Angiotensin II stimulates cardiac fibrosis and conduction heterogeneity.

Watanabe et al studied 3 different cohorts of patients:

I) 69 patients with paroxysmal lone AF

II) 151 patients with structural heart disease and no history of AF

III) 161 healthy subjects without cardiovascular disease or AF.

The ACE I/D polymorphism was associated with the PR interval and heart block in the lone AF cohort. In multivariable linear regression models, the D allele was associated with longer PR interval in the lone AF and heart disease cohorts. P-wave duration showed a similar trend, with increase in PR interval across ACE I/D genotypes in the lone AF and heart disease cohorts. The

ACE D allele is associated with electrical remodeling in patients with lone AF and in those with heart disease, but not in control subjects. ACE activity may play a role in cardiac remodeling after the development of AF and heart disease **([35])**.

Na(v)1.5, the main voltage-gated Na(+) channel in the heart, has been shown to be involved in many cardiac diseases. Genetic variants in the gene SCN5A, encoding Na(v)1.5, have been linked to various cardiac phenotypes, such as the congenital and acquired long QT syndromes, Brugada syndrome, conduction slowing (Lenègre disease), sick sinus syndrome, overlapping syndromes, dilated cardiomyopathy and even AF. Genetic studies have identified ion channel gene variants in families segregating AF, the most common arrhythmia in clinical practice. Variation in the SCN5A gene is not a major cause of familial AF **([36])**.

Mutations or rare variants in SCN5A may predispose patients with or without underlying heart disease to AF. This expands the clinical spectrum of disorders of the cardiac sodium channel to include AF and represents an important progress toward molecular phenotyping and directed rather than empirical therapy for this common arrhythmia**([37])**.

There is a positive, significant association between the minor allele rs2200733 T at chromosome 4q25 and patients with AF/atrial flutter (AFL) disease in a sample derived from the Italian population **([38])**.

The non-coding SNPs rs2200733 and rs10033464 are strongly associated with AF in four cohorts of European descent. A meta-analysis confirms the significant relations between AF and intergenic variants on chromosome 4**([39])**.

Channelopathies and genetic AF

I) Long QT syndrome

Compared to the background prevalence of 0.1%, early-onset AF was observed in almost 2% of patients with genetically proven LQTS and should be viewed as an uncommon but possible LQT-related dysrhythmia**([2])**.

LQT-3 variant is caused by gain-of-function mutations in the SCN5A encoding the cardiac Na^+ channel. Familial AF, previously considered a K^+ channelopathy, has recently been related to Na^+ genetic variants, both in isolated forms and in patients with underlying heart disease. Benito et al **([40])** reported an association of familial AF and LQT-3 due to a mutation in SCN5A. This finding provides further evidence of the role of SCN5A in AF. The authors also confirm the usefulness of flecainide in this particular complex phenotype, both as a diagnostic tool for LQT-3 and as an acute treatment for AF. During this month Makiyama et al **([41])**, identified in a Japanese family with

pseudo-lone AF a new phenotype resulting from the SCN5A gain-of-function mutations and is distinct from the LQT-3 variant. This caused a novel heterozygous gain-of-function mutation in the cardiac Na^+ channel gene, SCN5A. The mutant channels displayed a gain-of-function type modulation of cardiac Na^+ channels, which is a novel mechanism predisposing to increased atrial excitability and familial AF.

II) Andersen-Tawil Syndrome (ATS): It is considered LQTS 7. The entity **is** an autosomal dominant multisystem potassium channelopathy that affects the chromosome locus 17q23.1-q24.2 and gene mutation on *KCNJ2,* characterized by a clinical triad consisting of periodic paralysis, cardiac arrhythmia, and usually mild but diagnostically useful dysmorphic features. This channelopathy is due to mutation of the KCNJ2 gene encoding the protein Kir 2.1 with **ion current affected** potassium (I_{K1}). A missense mutation in KCNJ2 (encoding D71V) in Kir2.1 current as assayed by voltage-clamp.

QT prolongation associated with ATS is relatively benign in the clinic and the increase in transmural dispersion of repolarization, rather than QT interval, could be responsible for development of torsades de pointes **([42])**. LQTS patients have altered atrial electrophysiology: Atrial action potential durations (APD) and effective refractory periods (ERP) are prolonged in LQTS patients, and Polymorphic Atrial Tachycardias occurs. Polymorphic AT appears to be a specific arrhythmia of LQTS reminiscent of an atrial form of "torsades de pointes"**([43])**.

III) Brugada syndrome

Spontaneous AF and VF are closely linked clinically and electrophysiologically in BrS patients. Patients with spontaneous AF have more severe clinical backgrounds in BrS. SCN5A mutation is associated with electrical abnormality but not disease severity **([44])**. Sinus rhythm is the usual; however, Brugada Syndrome (BrS) patients exhibit an abnormally high proportion of atrial arrhythmias that are found in 10 to 25% of cases since the arrhythmogenic substrate is not limited to the ventricles. In the original discovery manuscript by the Brugada brothers (1992) **([45]),** temporary AF was mentioned, as well as by authors from Brazil **([46])**, from Japan **([47])**, and from Greece. These Greek authors verified an elevated incidence of paroxysmal AF in patients with spontaneous or induced type 1 electrocardiographic pattern of BrS and mention that the presence of atrial tachyarrhythmias may reflect an advanced stage of the disease. The prognostic significance of paroxysmal AF, particularly in asymptomatic patients with an ECG pattern consistent with BrS requires further evaluation. Physicians should always be aware of BrS in young patients with lone AF, especially in those with a history of syncope **([48])**. There is a more advanced disease process in BrS patients with spontaneous atrial arrhythmias and ventricular inducibility was significantly related to a history of atrial arrhythmias. The incidence of atrial arrhythmias in patients

with a spontaneous electrocardiogram of BrS was 26% vs. 10% in patients with a flecainide-induced ECG.

In patients with an indication of ICD, the incidence of atrial arrhythmias reached 27% vs. 13% in patients with BrS but without ICD indication.

Inappropriate shocks due to atrial arrhythmias episodes were observed in 14% of ICD patient's vs. 10.5% of appropriate shocks.

The implantation of a single-chamber device is an independent predictive factor of inappropriate ICD discharges. Careful programming of single-chamber ICD should be recommended to avoid inappropriate discharges in patients with BrS**(**[49]**)**.

Itho et al**(**[47]**)** mentioned that the paroxysmal form of AF is observed in a 30% of cases. A publication by Eckardt et al **(**[50]**)**, indicates a frequency for supraventricular arrhythmias of 29%. These authors described episodes of AV supraventricular tachycardia with reentry.

III) Congenital Short QT syndrome

Hereditary short QT syndrome is a clinical-electrocardiographic entity with autosomal-dominant mode of transmission and it is the most recently described channelopathy. The syndrome may affect infants, children, or young adults with strong positive family background of sudden cardiac death. Short QT syndrome is characterized by short QT and heart-rate-corrected QTc intervals. It is frequently associated with tall-, peaked-, and narrow-based T waves that are reminiscent of the typical "desert tent" T waves of hyperkalemia. There is a high tendency for paroxysmal AF due to the heterogeneous abbreviation of APD and refractoriness of atrial myocytes. The arrhythmia can also be induced by programmed electrical stimulation. Clinicians need to be aware of this deadly electrocardiographic (ECG) pattern as it portends a high risk of paroxysmal AF in young people and sudden cardiac death in otherwise healthy subjects with structurally normal hearts **(**[51]**)**.

The inherited short QT syndrome (SQTS) is a novel, genetically determined arrhythmia that resembles the pathophysiological counterpart of congenital long QT syndrome (LQTS). Gain-of-function ion channel mutations in cardiac potassium channel genes are the currently known cause of SQTS and obvious genetic heterogeneity is evident from the few reported families. At present, three subforms are known.

- SQTS type 1**(**[52]**)**
- SQTS type 2**(**[53]**)**
- SQTS type 3**(**[54]**)**

Gain-of-function mutations have been detected in three genes encoding potassium channels.

Most cases of familial AF are not caused by mutations in a single gene.

IV) Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

It is a condition that presents with exercise-induced syncope or sudden death in children or young adults primary therapy for CPVT is beta-blockade and implantable cardioverter defibrillator (ICD) placement. Despite appropriate ICD therapy, inappropriate ICD shocks are possible a consequence of paroxysmal AF **([55])**.

Gap junction mutation and Atrial Fibrillation

In the ventricles there is a great amount of connexins 43 and 45, while connexin 40 is not so numerous. The SA node and the AV node have only connexins 40 and 45, while in the atria there is a great amount of the three types; however, connexin 40 (Cx40) is the gap junction protein most found in atrial muscle tissue. A Cx40 expressed abnormally, increases the vulnerability and occurrence of atrial fibrillation and triggering in the formation of thoracic veins **([56])**. Gap junction therapy is aimed at improving conduction without affecting sodium channels and today it is considered a new pharmacological approach under investigation for the treatment of AF **([57])**.

Piatniski et al **([58])** developed a class of gap-junction modifiers typified by GAP-134, a compound currently under clinical evaluation. Selected compounds with the desired in-vitro profile demonstrated positive in vivo results in the mouse CaCl(2) arrhythmia model upon oral administration.

Recent research has found a variety of novel potential therapies related to Cx43 that can help to learn more about the mechanism of those cardiovascular diseases and the signaling pathway **([59])**.

Atrial Fibrillation associated with genetic structural heart disease

1) Familial Dilated Cardiomyopathy It is an underrecognized form. LMNA, encoding the nuclear membrane proteins, lamin A/C, was selected as a candidate gene for lone AF based on its established association with a syndrome of dilated cardiomyopathy, conduction system disease, and AF. LMNA mutations rarely cause lone AF and routine genetic testing of LMNA in these patients does not appear warranted **([60])**. Familial Lamin A/C deficiency is probably the most common cause of it. An animal model has shown that lamin A/C insufficiency causes apoptosis, particularly in the conduction system. Inheritance is predominantly autosomal dominant, but penetrance is variable. For symptomatic patients, the course is malignant, with AF, conduction system disease, heart failure, and sudden cardiac death **([61])**.

2) Hypertrophic Cardiomyopathy (HCM): In an unselected regional registry, AF was the major determinant of clinical deteriorations in patients with HCM **(**[62]**)**. The rate of inappropriate ICD shocks and frequency of device complications in HCM patients are not insignificant and are most common in younger patients and those with AF. Inappropriate ICD shocks are the most common device complication and should be accounted for when counseling high-risk HCM patients for ICD implantation **(**[63]**)**.

3) Idiopathic Restrictive Cardiomyopathy (IRCM): p.Arg721Lys mutation in the MYH7 gene. IRCM and HCM with restrictive physiology, both are part of the clinical expression of MYH7 and TNNI3 mutations and lead to worse clinical onset and progression of the disease with near 50% of AF **(**[64]**)**.

4) Arrhythmogenic **R**ight **V**entricular **D**ysplasia (ARVD):

ARVD is an uncommon inheritable cardiomyopathy that is familial in 30% to 50% of cases. The entity involves predominantly the right ventricle (RV) with progressive fibrofatty tissue replacement also in others cardiac chambers. A long-term follow-up (duration 8.5 years) analyzed typical ARVD patients (313 patients 197 males) from different primary and tertiary centers, and atrial arrhythmias were observed in 12%**(**[65]**)**. Balderramo et al **(**[66]**)** reported a case of ARVD in a 60-year-old man who developed sick sinus syndrome during evolution. Atrial arrhythmias may be explained by gradual replacement of right atrium myocytes by adipose tissue.

From a group of 126 patients with ARVD retrospectively analyzed for the presence of thromboembolic complications, i.e. pulmonary embolism (n=2), RVOT thrombosis with severe RV failure (n=1), and cerebrovascular accident associated with AF (n=2) were observed in 4% of the patients. Spontaneous echogenic contrast was observed in 7 patients with severe damage to the RV. In 4 of them supraventricular arrhythmias resulting in heart failure were reported. Annual incidence of thromboembolic complications was 0.5/100 patients **(**[67]**)**.

Implantable Cardioverter-Defibrillators (ICDs) therapy appears to significantly reduce mortality in selected patients with ARVD. Since ICDs are typically placed via a transvenous approach into the RV, there are complications associated with ICD placement and follow-up.

The ICD therapy appears to be well tolerated and important in the management of patients with ARVD([68]). The most common etiology of inappropriate therapy is AF with rapid ventricular response (68%), atrial flutter (13%) and sinus tachycardia (11%)([69]).

5) Unclassified cardiomyopathies: It includes a few cases that do not fit readily into any group (e.g., noncompacted myocardium, fibroelastosis, systolic dysfunction with minimal dilatation and mitochondrial disease.

Non-compaction cardiomyopathy, also called spongiform cardiomyopathy or isolated non-compaction of the left ventricular myocardium (INLVM).

Non-compaction cardiomyopathy (NCC) is a rare type of genetic cardiomyopathy ([70]) resulting from arrested myocardial development during embryogenesis. The entity is caused by mutations in LDB3 or "Cypher/ZASP"([71]). NCC can be easily diagnosed by characteristic appearance of prominent myocardial trabeculations and deep inter-trabecular spaces. The clinical manifestations include heart failure signs, AF, ventricular arrhythmias, and cardio-embolic events. It is considered a predictor of stroke together with, aneurysm, spontaneous echo-contrast and pulmonary hypertension. In these high-risk subgroups appears reasonable to use prophylactic anticoagulation. AF (9%) is related to extension of NCC ([72]).

6) Emery-Dreifuss Muscular Dystrophy (EDMD)

- Emery-Dreifuss muscular dystrophy (EDMD1) X-linked recessive inheritance with mutations in the STA gene on chromosome Xq28, > 70 different mutations which encodes a protein named emerin.
- Autosomal dominant EDMD (EMD2) due to mutations(>100 mutations) in the n lamin A/C gene (*LMNA)* gene that codes for lamins A and C on chromosome 1q21
- *SYNE1* mutations in the synaptic nuclear envelope protein 1
- *SYNE2* mutation in the synaptic nuclear envelope protein 2

CLASSIFICATION PROPOSSAL OF FAMILIAL ATRIAL FIBRILLATION

I) AF without apparent structural heart disease

- **Isolated: Only AF**
- **Associated with other channelopathy**

1. **Long QT-3 syndrome**

2. **Long QT-7 syndrome Andersen Tawil Syndrome (ATS)** near the inward rectifying potassium channel gene KCNJ2. A missense mutation in KCNJ2 (encoding D71V) in Kir2.1 current as assayed by voltage-clamp. The mutations in Kir2.1 cause Andersen's syndrome.

3. **Congenital short QT syndrome**

4. **Brugada syndrome**

5. **Catecholaminergic Polymorphic Ventricular Tachycardia**

6. **Lenègre disease.**

7. **Overlapping syndromes**

A) Monogenetic mutation

1) As an autosomal dominant tract or autosomal dominant inheritance pattern. (Only one copy of the defective gene -inherited from one parent- is sufficient to cause the disorder.)

- (1-a) Mutations in potassium-channel genes have been associated with familial AF but account for only a small fraction of all cases of AF. The loci that encode the subunits of potassium channels are.
  - Locus on chromosome 10q22-24
  - Locus on chromosome 1-q24.2
  - Locus on chromosome 1p36-p35
  - Locus on chromosome 4q25
  - Locus on chromosome 5p15
  - Locus on chromosome 6q14-16
  - Locus on chromosome 10p11-q21
  - Locus on chromosome 11p15.5
  - Locus on chromosome 17q23
  - Locus on chromosome 21q22.12.
- (1b) Mutations in sodium-channel: Recent research has shown that mutations in the gene encoding the cardiac sodium channel (SCN5A) is associated with AF
  - Locus on chromosome 3p.

2) As an autosomal recessive trait or autosomal recessive inheritance pattern. (An autosomal recessive disorder means two copies of an abnormal gene must be present in order for the disease or trait to develop.)

- Locus on chromosome 5p13

5) Mutations in genes that encode connexins/ gap junction

B) Mutations in multiple genes: Familial polygenetic predisposition.

II) AF associated with genetic structural heart disease (genetic cardiomyopathies)

1) Familial Dilated Cardiomyopathy (FDCM)
2) Hypertrophic Cardiomyopathy (HCM)
3) Idiopathic Restrictive Cardiomyopathy (IRCM)
4) Arrhythmogenic Right Ventricular Dysplasia (ARVD)
5) Unclassified:
   - Noncompacted myocardium, Non-Compaction Cardiomyopathy (NCC), Left ventricular hypertrabeculation/non-compaction (LVHT) or spongiform cardiomyopathy (Mutations in LDB3 or "Cypher/ZASP").
   - Fibroelastosis
   - Systolic dysfunction with minimal dilatation
   - Mitochondrial disease.
   - Emery-Dreifuss Muscular Dystrophy (EDMD)
     - Emery-Dreifuss muscular dystrophy (EDMD1) X-linked recessive inheritance
     - Autosomal dominant EDMD (EMD2)
     - *SYNE1* mutations in the synaptic nuclear envelope protein 1
     - *SYNE2* mutation in the synaptic nuclear envelope protein 2

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